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The MS Process and Targets for Treatment

A look at the immune system in MS and disease-modifying therapies

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The MOTIVATOR

Published by the Multiple Sclerosis Association of America

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706 Haddonfield Road
Cherry Hill, New Jersey 08002
(800) 532-7667
www.msassociation.org

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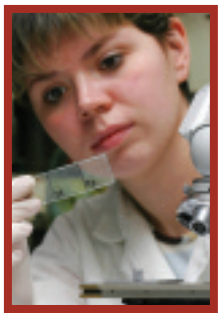


COVER STORY

DEPARTMENTS

MSAA™ Multiple Sclerosis Association of America

The Multiple Sclerosis Association of America's mission is to enrich the quality of life for everyone affected by multiple sclerosis.

Up Front

By Douglas G. Franklin
MSAA President and CEO

Douglas G. Franklin

The year 2010 is proving to be a challenging economic environment for all charities, as people throughout the country adjust to the financial challenges brought on by this recession. Much of MSAA's direct marketing efforts have been affected by the downturn and many supporters have expressed their hope that despite the tough times, we will continue to operate our programs and services to help people with MS enrich their quality of life. This is certainly a challenge that our Board members at MSAA have supported and everyone is working hard to keep the association strong.

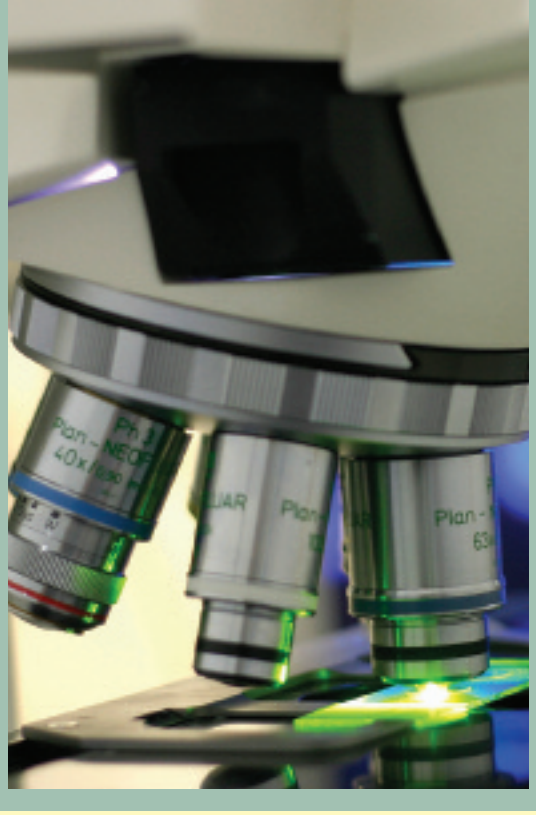
I had the privilege of supporting our two snowmobile charity runs this year. Both TransMontana and TransWyoming were great successes and everyone involved with these events is to be commended for a job well done. So many people help make them a success and it's gratifying to see such dedication for a cause as important as MS. We are also embarking on an ambitious series of independent volunteer fundraisers, including our "Swim for MS" events to help support our programs and services. It's wonderful to see the enthusiasm of these grassroots efforts!

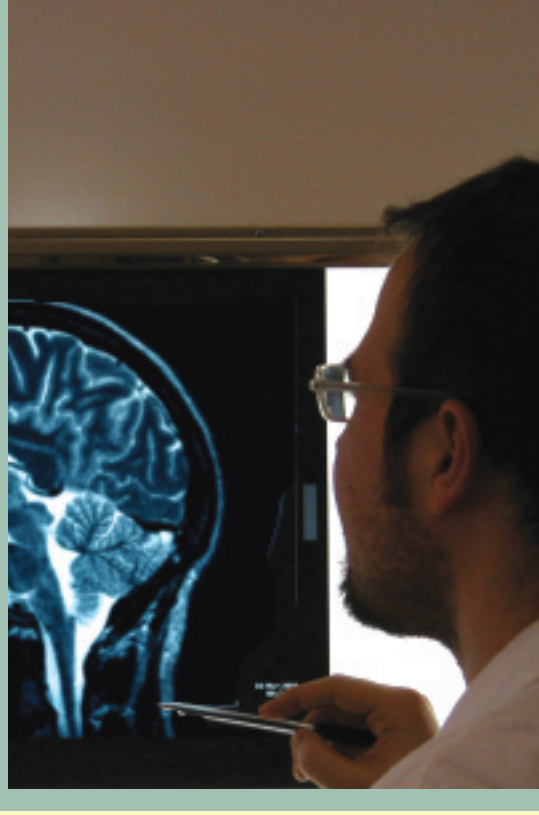
We want to thank everyone for supporting MSAA and helping us to be there for our MS constituency, both for today and for tomorrow.

March was MS Awareness Month. In addition to leading the MS Coalition's active participation in the Public Policy Conference in Washington, DC, hosted by the National MS Society, MSAA sponsored a number of public-education events across the country. These highlighted MS-related topics while promoting wellness and life enrichment.

Adverse times require renewed commitment to action and change. MSAA has always been willing to find flexible solutions to keep our program offerings strong. In times like these, our MS constituency needs us more than ever and we want to thank everyone for supporting MSAA and helping us to be there for them, both for today and for tomorrow. ◆

Doug Franklin joined MSAA as President & CEO in 1999. He has a distinguished career in nonprofit leadership and is a former national trainer in strategic planning for the Peter Drucker Foundation. A published international expert in social marketing and corporate social investment, he is a graduate of four universities. He currently serves on the National Board of the Key Philanthropic Organizations Committee of the American Society of Association Executives; on the Executive Committee of Health First – America's Charities Board in Washington, DC; and as President of the Multiple Sclerosis Coalition.





The MS Process
and Targets for Treatment

A look at the immune system in MS and disease-modifying therapies

written by **Susan Wells Courtney** and **Jack Burks, MD**

The disease processes occurring with MS are both complex and confounding. Over the past century, details about this disease have been ever-changing, as larger, more rigorous trials and better technology have led to new findings and a greater understanding of what takes place within the central nervous system of individuals with MS.

Much of what researchers have learned comes from observations of lesions (or plaques) in the brain, the hallmark feature of MS and the reason behind the name "multiple sclerosis," meaning "many scars." Lesions are areas of inflammation along the nerves in the brain and spinal cord. When the inflammation remits, these areas of damage may either partially repair or form a permanent scar.

While very early studies relied on post-mortem examination of the brain and lesions for initial clues about the disease, highly advanced diagnostic tools and procedures are able to give scientists an inside view of the intricate components found with the lesions and surrounding areas of the brain and spinal cord. In addition to improved magnetic resonance imaging (MRI)

techniques, other technical advancements include magnetization transfer imaging (MTI), spectroscopy, and functional imaging. Analysis of the spinal fluid is also helpful in showing evidence of the disease process taking place.

Where Does MS Damage Occur?

Of the countless variables involved, scientists know that MS is a chronic condition, whose effects are limited to the central nervous system (CNS), consisting of the brain, optic nerves, and spinal cord. The areas of inflammation, damage, and scarring, are referred to as lesions (or plaques). These are most often found in periventricular regions (around blood vessels) of the brain, but also occur in the optic nerves, brainstem, and spinal cord.

The effects of MS in the brain are also more far-reaching than originally thought. Axons, which are the wire-like nerve fibers with a protective myelin covering, are found in the white matter of the brain. This is where lesions are usually found and the damage was thought to be limited to this area. Normal-appearing white matter (NAWM) refers to areas of white tissue in the brain that occur around and between lesions. An axon is just one part of the entire CNS nerve cell, called a neuron, which also has a cell body. The neuron's cell body is usually in the gray matter of the brain, which is a layer of cells covering the white matter. The effects of MS are now known to reach many areas of the brain, including white, gray, and normal-appearing white matter.

The damage seen in MS lesions was initially believed to involve only the myelin of the CNS. Myelin is a fatty protein that serves as a protective covering to the nerves that carry messages to and from the brain. These nerves are similar to electric wires, with their ability to carry electrical impulses and their need for a protective covering, so no electrical impulses are lost. Newer studies found that damage to the nerves (or axons) themselves occurs early in the disease, frequently in advance of any clinical (outward) symptoms experienced by the patient. This damage to the myelin and axons is what causes the many symptoms associated with MS.

MS is often "clinically silent," meaning that disease activity is taking place internally, while no new signs or symptoms of the disease are experienced externally, i.e., clinically. In addition to outward symptoms and changes in function, disease activity is measured by the number, size, and inflammation of lesions, as seen on an MRI.

Types of MS

The majority of patients (85 percent) begin with a relapsing-remitting form of MS (RRMS). With this type, individuals experience symptom flare-ups (also referred to as "exacerbations" or "relapses"), lasting from a few days to a few months. Corresponding flare-ups of inflammation and lesion formation may be viewed on an MRI. These are followed by a complete or partial remission, which for many, can last for months or years.

This remission can be deceptive, however, because of the clinically silent aspect of MS. Lesion flare-ups and inflammation within the CNS occur at least 10 times as often as clinical attacks. Without the benefit of an MRI, patients and medical professionals can only identify outward symptoms and clinical attacks, and are not aware of the degree of disease progression within the CNS.

Without treatment, many people with RRMS will eventually advance to secondary-progressive MS (SPMS). They may either experience relapses with less recovery, or have no relapses at all. Primary-progressive MS (PPMS) patients (10 percent of the MS population), have fluctuations of symptoms, but no documented relapses. Progressive-relapsing MS (PRMS) patients (less than 5 percent of the MS population), experience progression from the beginning, but also have superimposed relapses. Progression indicates a gradual course of nerve degeneration, with less involvement of inflammation in the disease process.

MS Inflammation and Degeneration

The damage seen with MS appears to be an integrated two-part process, involving both inflammation and degeneration. Acute relapses result from acute inflammation and axonal demyelination. Disease progression reflects neurodegenerative processes, such as axonal/neuronal damage and brain atrophy.

Much of the disease process is thought to be caused by inflammation – which is the body's natural defense against disease and foreign bodies. Inflammation occurs as disease-fighting cells, such as T and B lymphocytes, as well as other components of the immune system, wage an attack on the invaders. Since the mid-1900s, researchers have found evidence to support the idea that MS is an autoimmune disease – one in which the body's own immune system attacks the body – in this case, the myelin and nerves of the CNS. To reach the CNS, the lymphocytes must cross the vital blood-brain barrier (BBB), a wall that lines the blood vessels and normally prevents such damaging cells from entering the brain and spinal fluid.

If MS is an autoimmune disease, some unidentified factor has caused the immune system to become activated and misdirected. Such a cause is still a mystery, although evidence grows to support a number of different possible theories. A complex genetic predisposition appears to be involved, with a slightly increased risk for close family members.

Environmental factors also come into play. Among others, these include: how far a person lives from the equator and one's lack of exposure to vitamin D (naturally derived from sunlight and certain foods); cigarette smoking, pollutants, and other toxins; various diets, including a high intake of saturated fats and/or a low intake of fish oils; as well as viral or bacterial infections. With regard to viral infections, the Epstein-Barr Virus (EBV) appears to have the most evidence as a possible trigger for MS, perhaps following several years of dormancy. Most people are exposed to EBV, a common herpes virus that is often asymptomatic in children.

However, EBV can cause mononucleosis in approximately half of the adolescents and adults affected.

Molecular mimicry is one possible reason for the immune system's attack in MS. This could happen when a foreign protein entering the body has a very similar structure to the myelin's fatty protein structure. As the T cells are activated and target the foreign protein for destruction, they become misdirected and also attack the myelin. Such a case of mistaken identity would explain why the body's own myelin and CNS are under attack. Viruses may initiate an autoimmune disease in this fashion. Examples of viruses with a similar structure to myelin include measles, influenza, Epstein-Barr Virus (EBV), and other herpes viruses.

A recent theory explores a possible connection between chronic cerebrospinal venous insufficiency (CCSVI) and multiple sclerosis (MS). CCSVI is a complex condition involving a decrease of blood flow from the brain back to the heart, which some researchers theorize could possibly lead to activation of the immune system, excess iron deposits, loss of myelin, and other nervous system damage. (This theory and related studies are discussed in the Research News column of this issue of *The Motivator*. Please refer to page 26 for more information.)

For many years, with the assumption that MS is an autoimmune disease, the inflammation (brought on by the body's immune system) was thought to come first, followed by resultant degeneration (or damage) caused by this inflammation. New studies have found some evidence that this order may be reversed. This would mean that the degeneration may occur initially, followed by inflammation in an effort to fight whatever is causing the initial damage.

Details from a study in Sydney, Australia, were published in the article, "Multiple sclerosis: distribution of inflammatory cells in newly forming lesions." (Henderson AP, Barnett MH, Parratt JD, Prineas JW; *Annals of Neurology*, 2009 December; 66[6]: 739-53.) In this study of 26 active lesions from 11 patients with early MS, the researchers found that the lymphocytes involved in inflammation are absent from early lesions. These lesions showed loss of oligodendrocytes (cells that make myelin) as well as areas of degenerate and dead myelin, along with myelin phagocytes (cells that clean away the dead myelin). Conversely, areas of complete demyelination were "packed" with lymphocytes and other immune-system cells creating inflammation. Some of these advanced lesions also had oligodendrocytes, working to regenerate myelin.

The findings from this study suggest that inflammation may not be the first step in the formation of lesions, and destructive cell-mediated immunity does not cause the initial damage to myelin or oligodendrocytes. The autoimmune response may be a reaction to the damage, and not the cause of the initial attack. If this theory holds true, it will mean that some other factor is causing the initial damage and formation of lesions, and the MS process is not initiated by an autoimmune attack on the CNS. Any of the suspected

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causes listed earlier may still play a role. More research is needed to confirm these findings, but this study is another important piece in the complex puzzle of MS research and treatment development. If this new theory is correct, current disease-modifying therapies (DMTs) would still be helpful.

Disease-Modifying Therapies

A number of disease-modifying therapies (DMTs) have been developed to interrupt the different stages of the disease process, in an effort to minimize inflammation and lesions, clinical attacks, and the progression of disability. Targets include reducing inflammation and damage by blocking the action of lymphocytes, redirecting the attack of these immune-system cells, preventing these cells from crossing the BBB into the CNS, or other therapeutic strategy. Some of these DMTs have been in use since the early 1990s and have been shown to reduce relapses, slow disease activity, and delay the progression of disability.

These drugs have been of tremendous help to many individuals with relapsing forms of MS, but their use is limited. For instance, not everyone responds to the treatments presently available, particularly individuals with progressive forms of the disease who do not experience disease flare-ups. Side effects, such as flu-like symptoms or injection-site reactions, may prevent some individuals from being able to tolerate these treatments. Others may not have adequate insurance coverage needed to afford these treatments. Additionally, newer drugs used as DMTs have severe adverse events associated with them, and patients must be closely monitored.

Despite any limitations of the presently approved long-term treatments for MS, they still hold great value for many members of the MS community in delaying or preventing disease activity. Most of the DMTs have an excellent safety profile after many years of use, which is reassuring for those on long-term therapies. And the good news for everyone is the fact that research continues at an exciting pace. New details about the disease are constantly being discovered, which provide new targets for treatment.

Dozens of experimental drugs and treatments are under development, with several in later-stage clinical trials. While the presently approved DMTs are given via self-injection at one's home, or through infusions at medical facilities, several oral medications are now being studied. Gilenia (FTY720) and oral Cladribine are two drugs presently being reviewed by the United States' Food and Drug Administration (FDA), while other oral drugs are in late-stage clinical trials.

The Immune System and MS

The Body's Defense

The body's defense against disease and infection is the immune system. It is incredibly complex, and using an analogy, it may be thought of as an army of soldiers who are ready at a moment's notice to defend against any invader that may pose a threat to the body's good health. This army has many members who play different roles.

Of course, the system includes plenty of disease-fighting warriors who attack invading viruses, bacteria, other foreign bodies, or malignant cells involved in cancer (all of which are known as "antigens"). It also has cells that act like generals to instruct the soldiers when to go to battle, as well as those that act like military police, or "MPs," who tell the warriors when to settle down and when to retreat. The body's defense system even has "detectives" which circulate throughout the body, searching for any invaders that do not belong there. This wonderful policing system helps to keep people healthy throughout their lives. Without the immune system, a person would not survive a simple infection.

The members of the defense system's army are constantly aware of what they recognize as "self," and what they recognize as "non-self." This system is designed to protect the tissues and organs which are a natural part of the body – and are recognized as "self." Its army of soldiers circulates through the blood system in a peaceful manner, and the soldiers are kept away from vulnerable areas of the brain and spinal fluid by the blood-brain barrier, which lines the walls of the blood vessels.

When a non-self entity is spotted, such as a virus, bacteria, or foreign tissue from a transplanted organ, the army is called to action. When this happens, many types of cells, molecules, chemicals, and proteins are produced – all in an effort to rid the body of the foreign invader. The fighters rush to the area of infection, causing inflammation and swelling at the site of attack.

This is where the system becomes quite complex and specialized, as messages are passed from cell to cell. Adhesion molecules work like a key to open the blood-brain barrier (BBB) and allow the disease-fighting soldiers into the fragile CNS, giving them access to the brain and spinal fluid. Chemicals bind to the foreign antigen through matching receptors, and these foreign antigens are then presented by "antigen presenting cells," or "APCs," to the immune system cells, or soldiers, so they may recognize and destroy them.

Macrophages are cells that are constantly on "KP duty," and they are sent in to clean up what is left of the destroyed enemies. And while this war is being waged on the invading entity, tissues recognized as "self" are normally protected and remain untouched. Confusion arises if a foreign antigen looks too much like "self" tissue.

With autoimmune disorders, the body's defending army malfunctions and perceives certain "self" tissue as the enemy. It may be a case of mistaken identity, or molecular mimicry, where the cells of the immune system initially locate an antigen (foreign invader) which happens to have a similar molecular structure to a part of the body's own tissue.

If not mistaken identity, the attack could be a result of overly aggressive soldiers (immune system cells), or perhaps those cells designed to suppress the aggressiveness of the fighter cells are short in supply, or not doing their job. Genetic factors are thought

to be involved with the malfunction, and other causes such as a defect in the myelin, could also play a role.

Another area of interest concerns astrocytes, which are star-shaped cells found in the nervous system. These are believed to be involved with different functions, including the conduction of nerve impulses and response to injury. The potentially changing role of astrocytes and MS is being researched intensely by some scientists.

A great deal is known about the immune system, but researchers do not know if the immune system's initial attack is the "cause" or a secondary "effect." All agree that the immune system plays an important role in MS and current FDA-approved treatments are advantageous in most patients.

Features of the Immune System

The immune system is extremely complex and includes far too many components to mention all of them in this article, so to follow are some important features of the immune response. Many of these terms are identified in articles on the approved disease-modifying therapies for MS, as well as emerging therapies in clinical trials.

The defense system is set up to respond to a foreign entity (or antigen) in two different ways. The first type of reaction is the innate immune response, and the second type of reaction is the adaptive immune response. The actions of both responses are needed to work together for the best protection against foreign entities and disease.

The "innate" or "natural" immune response is nonspecific. It does not have any type of memory, and reacts in the same way each time it encounters a foreign entity, such as a virus or bacteria. Even if the exposure is to the same germ, the innate response has no memory and its reaction will not change. This type of immune response is quick to react to a foreign invader and is first on the scene to protect the body.

Several types of "soldiers" take part in this initial attack. They include neutrophils, monocytes, and macrophages. They work by engulfing and digesting foreign invaders (a process known as "phagocytosis"), and they also clear up dead cells and debris. Natural killer (NK) cells destroy the enemy by rupturing the plasma membrane. This destruction is known as "cell lysis."

The "adaptive" or "active" immune response is specific. While this type of defense initially responds slowly, it has a memory, and with each repeated exposure, the reactions become faster and stronger. The adaptive immune response reacts with both T-cell and B-cell lymphocytes, also referred to as T cells and B cells.

The different classes of T cells secrete chemicals or mature into cells that regulate other cells, helping to either increase or decrease inflammation. To become activated, T cells require an antigen-presenting cell (APC) to present the foreign antigen; otherwise, the T cell cannot recognize it. The APCs must break the antigens down into smaller pieces, and some of these smaller pieces are associated with genetically determined major histocompatibility

complex (MHC) proteins in the APC. T cells are only able to recognize foreign antigens when they are with MHC proteins on the surface of APCs.

CD4+ and CD8+ cells are the two main types of T cells. Here is where the recognition of the MHC proteins on antigen-presenting cells (APCs) comes into play. CD8+ T cells only recognize class I MHC proteins (expressed on almost all nucleated cells). The CD8+ cells can then implement the direct destruction of the foreign antigen. CD4+ T cells only recognize class II MHC proteins (expressed on specific APCs, such as macrophages, dendritic cells, and B cells).

When activated, the CD4+ cells differentiate, or mature into four different subsets of T cells: (1) Th1 cells are pro-inflammatory and secrete cytokines IL-1, IL-2, interferon (IFN) gamma, IL-15, tumor necrosis factor alpha (TNFA), and other elements; (2) Th2 cells are anti-inflammatory and secrete cytokines IL-4, IL-5, IL-6, IL-10, and IL-13; (3) Th17 cells are pro-inflammatory and produce the cytokine IL-17 and other elements; (4) T-regs are regulatory; they are able to suppress the function of pro-inflammatory T cells; In this manner, T-regs help to protect against autoimmune disorders.

MS Treatments and Their Mechanisms of Action

This entire article is aimed at providing a better understanding of the MS disease process, the disease-modifying therapies, and targets for treatment. The following chart lists the approved disease-modifying therapies for MS, and several (but not all) of the experimental drugs for MS in later-stage clinical trials, along with their mechanisms of action.

Much of the information was taken from MSAA's Summer 2009 issue of The Motivator, "MS Research Update 2009," by Dr. Diana M. Schneider. The full article may be viewed or downloaded by visiting ***www.msassociation.org****, and then selecting "Publications," "The Motivator," and the "Summer 2009" issue. Readers without internet access may request a copy by calling MSAA at* ***(800) 532-7667****.*

FDA-Approved Medications

Avonex® and Rebif® (both interferon beta-1a) as well as Betaseron®and Extavia® (both interferon beta-1b) reduce disease activity through a number of mechanisms, including the reduction of T cell inflammatory activity (Th1 cells). This reduces the number of T cells that damage myelin. They also stabilize the BBB, which helps to keep damaging cells out of the brain. The interferons also perform other positive actions as well.

Copaxone® (glatiramer acetate) is a mixture of four amino acids found in myelin basic protein, which is a key component of the myelin sheath that is damaged in MS. It diminishes several of the damaging MS disease processes, including the promotion of a shift in Th1 cells (pro-inflammatory) to Th2 (anti-inflammatory) responses. Copaxone increases T-regulatory cells that reduce immune system damage. It may also improve nerve function in the brain by increasing brain-derived neurotrophic factor (BDNF), which may provide neuroprotective effects.

Novantrone® (mitoxantrone) is an immunosuppressant that has been used for years to treat cancer. It targets rapidly dividing cells, including those believed to be involved in MS.

Tysabri® (natalizumab) is a laboratory-produced monoclonal antibody that prevents lymphocytes from migrating across the BBB and into the central nervous system (CNS). Recent data suggest that it may also enhance remyelination and stabilize damage to the myelin sheath. These and other results suggest that the drug may improve CNS function.

Experimental Monoclonal Antibody Medications

Campath® (alemtuzumab) is approved for the treatment of B-cell leukemia and targets T cells, B cells, and macrophages.

Rituxan® (rituximab) binds to a molecule on the surface of B cells and depletes them from the circulation.

Zenapax (daclizumab) is a genetically engineered antibody against a substance necessary for the growth of T cells. It results in a sustained but reversible reduction in activated T cells, and turns off inflammation.

Experimental Oral Medications

Cladribine causes a preferential and sustained depletion of specific classes of T cells in the immune system. It also reduces the overall T-cell inflammatory response.

Gilenia® (Fingolimod, FTY720) blocks potentially damaging T cells from leaving lymph nodes, lowering their number in the blood and tissues, including the CNS. It may reduce damage to nerves and enhance nerve repair. It also increases certain T-reg cells (which favorably regulate the immune system), and may promote a shift from Th1 (pro-inflammatory) to Th2 (anti-inflammatory) responses.

BG00012 (BG 12; fumarate; fumaric acid esther) may have a distinct dual mechanism of action. It modulates the immune system and has anti-inflammatory properties, as well as reduces the damaging macrophage activity. It may also have neuroprotective effects. This is due to its activation of a substance that increases the resistance to cellular damage from what is termed "oxidative stress."

Laquinimod modulates the immune system and is an anti-inflammatory agent. From animal studies, it reduces infiltration of macrophages and CD4+ cells across the BBB and into the CNS. It also promotes a shift from Th1 (pro-inflammatory) to Th2 (anti-inflammatory) responses.

Teriflunomide modulates the immune system by reducing the division of harmful T cells. It disrupts the DNA of rapidly dividing cells, which results in antiproliferative effects.

Statins are oral medications most commonly prescribed to lower cholesterol. Their anti-inflammatory properties have stimulated more clinical trials in MS.

Additional Therapies Being Studied

Tovaxin® is a T-cell vaccine where T cells are removed from a small amount of the patient's blood and then are grown in a test tube environment (where they increase in number). These T cells are inactivated, and then injected back into the patient. As a result, the immune system is stimulated to recognize and eliminate the inactivated cells as well as active damaging cells.

BHT-3009 is a DNA "vaccine" containing a gene for myelin basic protein (MBP). The vaccine coats the MBP and induces immune system tolerance. This action limits the response of specific damaging immune cells involved with MS, thereby reducing the attack against the MBP in MS patients.

Vitamin D3 studies show that an inverse relationship appears to exist between vitamin D3 levels and the probability of developing MS. Proteins activated by vitamin D bind to and alter the function of a section of the chromosome near a specific gene variant which increases the risk of MS, suggesting that vitamin D deficiency during pregnancy might alter the function of fetal genes.

Tetracycline Antibiotics including minocycline and doxycycline, have immunomodulatory and neuroprotective activities. They also appear to decrease the passage of leukocytes across the blood-brain barrier.

Many immune-system cells secrete cytokines and chemokines. Cytokines are small proteins that may stimulate or inhibit the function of other cells. They connect to specific receptors found on the surface of cells, and send messages from one cell to another. More than 100 cytokines have been discovered within the past decade; they include interleukins (IL); interferons (INF); tumor necrosis factor alpha (TNFA), transforming growth factor (TGF), and more.

Chemokines are very small cytokines that direct the T and B cells to areas where inflammation or injury is taking place. Scientists have found more than 50 chemokines, and these are categorized into families, identified as C, CC, CXC, and CX3C.

The complement system is another important part of the immune response. This system has many proteins which circulate as inactive molecules, and become activated once the immune system's antibodies have joined up with invading antigens (foreign bodies). From here, the "complement cascade" begins, increasing inflammation. Normally, this mechanism is helpful in eliminating foreign antigens. In MS, they can be misdirected to damage normal "self" brain tissue.

B cells produce immunoglobulins (Ig), which are usually antibodies aimed at fighting disease and infection. Immature B cells interact with T-helper cells to mature into memory B cells (where Ig is expressed only on the surface), or plasma cells (which secrete large amounts of Ig). This ensures a rapid response to recurrent foreign antigens. Recently, the role of B cells has been recognized as a major factor in the formation of MS lesions.

An Overview of the MS Process

Much MS research has focused on the development of the MS lesion. The process is believed to originate from activation of CD4+ cells specific for myelin antigens in genetically susceptible individuals. This activation enables these cells to enter the CNS through changes in the BBB. Activated T cells migrate into the CNS across the BBB through a step-by-step process, which includes binding to the vascular cell adhesion molecule-1 (VCAM1).

Once in the CNS, the T cells are then reactivated when they recognize myelin antigens on the surface of local APCs. This triggers pro-inflammatory cytokine release and a cascade of events leading to the formation of an inflammatory, demyelinating lesion. Many other cell types are included in the process, such as CD8+ cells, B cells, activated macrophages, microglial cells, complement, immunoglobulin antibodies, and more. A lack of sufficient T-reg cells, which usually keep the immune system from over-reacting, also contributes to lesion development. In active MS lesions, a perivascular infiltration of CD4+ cells, CD8+ cells, monocytes, and B cells occurs, with the eventual appearance of macrophages. Both Th1 cells and Th17 cells promote inflammation, while Th2 cells reduce inflammation.

MS Targets and Treatments

Targets for MS treatments include the many components and functions of the immune system response. In general, treatments have been developed to reduce or deplete those cells and other agents that promote inflammation and/or damage the CNS. Examples of these include T cells, B cells, monocytes, macrophages, dendritic cells, leukocytes, chemokines, cytokines, complement, and others. Specific targets for reducing inflammation include shifting the response from Th1 (pro-inflammatory) to Th2 (anti-inflammatory) as well as the enhancement of T-regulatory cell function.

Interrupting this chain of events also includes preventing the damaging cells from entering the CNS through the BBB. Researchers approach this by developing methods to limit the number of T cells circulating in the blood system, so they do not cross the BBB. Another approach is to interfere with the recognition of the adhesion molecules, so T cells cannot bind to them and subsequently pass through to the CNS.

In addition to the treatments which are FDA approved or in development to limit or stop the MS process, treatments are also being developed for neuroprotection and remyelination. Such strategies would protect the axons and myelin from further damage, and could potentially return lost function for individuals with MS. The future looks bright as science continues to discover more about the immune system and MS. ◆

Ask the Doctor

By Dr. Jack Burks
Chief Medical Officer for MSAA

Spinal Cord Lesions vs. Brain Lesions

Dr. Jack Burks

Q: Do spinal cord lesions affect body function and disability the same as lesions found in the brain?

When I was first diagnosed three years ago, my neurologist stated that he had "never seen so many lesions on a spinal cord," which I was terrified of hearing. About 30 percent of my spinal cord has lesions, but I don't have any lesions in my brain. I am scared that the spinal cord lesions will lead to not being able to walk. So far, all of my exacerbations have been with my eyesight and vertigo – nothing yet affecting my legs.

In your experience, is there more significant disability in terms of mobility linked to spinal cord lesions compared to brain lesions, and vice versa? Have there been any studies regarding the location of lesions?

A: As in your situation, sometimes the correlation of the specific abnormal findings on the neurological examination may not be reflected on the brain and spinal cord MRI. This works both ways. For example, sometimes MS lesions on the MRI are very numerous and the exam is relatively normal. Conversely, sometimes we see very few MRI lesions in MS and the person has significant disability. In other words, the MRI in MS is less precise than one might expect. In contrast, with stroke patients, the MRI lesions correlate very well with the clinical signs. One explanation is that, in MS, the myelin can be partially damaged by the inflammation seen on the MRI, but not totally destroyed. Therefore, the "messages" can still get through enough to function. In stroke, the damage is more complete, so the MRI is better correlated with the examination.

However, MS expert neurologists believe that many lesions on MRI still constitute a serious situation because the increasing damage will likely take its toll eventually. We have found that the amount of MRI damage in MS patients may likely predict future trouble.

Although not always (as in your situation), the MRI lesions in the spinal cord usually have a better correlation with a neurological exam than MRI brain lesions. When I evaluate MS patients who say "30 percent of my spinal cord has lesions on MRI," I highly recommend they be on an MS treatment to reduce the inflammation.

To answer your question, in general, spinal cord lesions are more likely to be correlated with mobility-related disability than brain lesions. You are correct to be concerned about future walking problems. Spinal cord lesions are often associated with weakness and spasticity (stiffness) in the

arms and/or legs, along with numbness or tingling. Problems with bladder, bowel, and sexual function may also occur.

I have one last comment. I suspect you have MS. However, since you have visual problems and spinal cord lesions, I suggest you talk to your doctor about another disease called Neuromyelitis Optica (NMO) or Devic's Disease. This disease primarily affects the eyes and spinal cord. A blood test (NMO antibody) is available. Devic's Disease usually has prominent spinal cord symptoms, but not always. Also, the treatment is different than for MS.

Q: During the holidays, I cut myself while opening a ceramic gift that was broken in transit. I could not feel that I was cut, nor did I notice how much I was bleeding from the minor wound (which was soon remedied with a bandage). How does absence of sensation fit in with not noticing a great deal of bleeding visually?

Similarly, I now have a habit of losing things that are in my hand. I have had to purchase several duplicate car keys to ensure that I may drive my car. Diving in the dumpster and trash can to retrieve lost items is not new to me. Could you fill me in on how the loss of sensation relates to other things?

I try to be organized and put things in specific places, which helps to a degree. But I have a difficult time when I am holding things. Any insights would be greatly appreciated.

A: Your letter illustrates the many facets of MS symptoms, including visual disturbances, loss of sensations, problems with organizational skills, and memory difficulties. Your problems stem from scarring in multiple areas of the brain (which is how multiple sclerosis was named).

While we do not have the MS "cure" and do not have adequate drug treatments for some MS symptoms, there are programs to help people with MS to compensate and adjust to various symptoms. These may help individuals to maintain their productivity and quality of life.

For example, rehabilitation programs are designed to improve one's function, even in the face of increasing symptoms. Cognitive (memory) rehabilitation, physical therapy, occupational therapy, and speech therapy are examples of specific interventions that are aimed to enhance body and mind function in MS. You have already discovered some ways to help compensate for some of your problems (such as losing things). Your doctor can help you explore other options as well.

Q: I was diagnosed with MS recently and my doctor recommended that I start on Copaxone. Are there any studies on the long-term effect of this medication? Have there been people who have been on the drug for five years, 10 years, or more, who have been studied for their overall health? Also, if a person starts on the medication and for some reason stops at a later date (one year, two years, etc.), have there been studies as to whether the lesion progression

increases markedly more than would normally occur?

A: Your question is timely. Researchers have recently published results after studying people continuously while they have been on Copaxone® treatment for 15 years. These results were terrific news for these patients and confirmed earlier observations. People on Copaxone were usually doing very well after 15 years. In addition, it was very safe and was well tolerated.

Specifically, more than 80 percent of patients treated with Copaxone for 15 years were still walking without any assistance, even though they had MS for an average of 22 years. Their MS relapse rate decreased by 78 percent, and two-thirds did not go on to progressive MS. This is a much greater portion than predicted for untreated patients. This good news further encourages me to help people stay on therapy for the long run. Remember, current MS medications do not continue to work, unless you stay on the treatment. Discontinuing any disease-modifying therapy that has some positive effect, will likely lead to a return of disease activity if no other treatment is prescribed. No data is available to indicate that lesion progression increases markedly more than would normally occur, when discontinuing Copaxone.

The long-term trial results tell us something else that is very important. The people who were on placebo at the beginning of the clinical trial also did well when they were switched to Copaxone after the trial. However, they lost some ground by being on a placebo for a short time – and they never caught up. One lesson learned by these data is to begin therapy early for maximum benefit.

Studies with the other MS disease-modifying therapies (DMTs), specifically the interferons (Avonex®, Betaseron®, Extavia®*, and Rebif®), also show that people on treatments for a long time did well. Individuals lost ground if they did not start therapy early. Two other DMTs, Novantrone® and Tysabri®, have several years of study behind them as well to support their effective use in treating MS. Novantrone may only be used for a maximum of two to three years, due to potential heart problems and leukemia risks. Tysabri requires close monitoring to watch for a rare but serious viral infection.

(*Please note that although the second brand of interferon beta-1b, Extavia, has not undergone years of research, it is the same medication and dosage as Betaseron, which has been studied extensively and has been prescribed since the early 1990s.)

Further, these data suggest that being off of a disease-modifying MS therapy for a significant time period is not a good idea. More ground may be lost. That is why we usually switch therapies, if there are problems, rather than discontinue all MS medications. We have learned that the current MS treatments do not work as well if we wait to start them later in the disease course.

Q: I have a combination of medical problems and have found that I need some

help with recognizing if or when I am having a relapse. With respect to other conditions, I have had ear problems since 1972. These cause imbalance, dizziness, and the feeling of being pulled to the left or falling forward. I also have a tarlov cyst on the sacral spinal canal favoring the right side, and this causes tingling down the right leg. Additionally, I have arthritis which causes pain in the back and legs.

I know that these can also be signs of an MS exacerbation, so when these symptoms are acting up, I don't know if I am having a relapse or not. Could you please give me some ideas on how I might be able to separate other problems from those caused by MS?

I have a second question as well. Every cholesterol medicine I have taken (Crestor®, Lipitor®, Zetia®) seems to cause my symptoms to act up. Is there a cholesterol medicine that I may be able to better tolerate, and may not increase my symptoms?

A: To answer your first question, multiple illnesses with overlapping symptoms can create a challenge for the neurologist. The key difference is that the changes during an MS exacerbation are usually very specific on the neurological examination and the MRI. The neurologists and neuroradiologists (MRI experts) are well trained to separate these differences. While the symptoms may be similar, the exam and/or MRI are usually different for the different diseases. But not always! My advice is to consult your neurologist if you think you may be having an MS flare-up, as he or she is the best person to determine the cause of your symptoms.

To answer your second question, cholesterol medications do not increase MS symptoms in most MS patients. In fact, recent data indicate a positive effect by statins in MS patients. However, some controversial research (the results are not supported in other studies), indicates that statins, which are cholesterol-lowering drugs, can interfere with interferon therapy. The interferons include Avonex, Betaseron, Extavia, and Rebif.

Unfortunately, you feel that Zetia, a non-statin drug, also causes an increase in MS symptoms. There may be something else going on, so your doctor should be aware of any changes in your symptoms. Ask your doctor about other ways to lower your cholesterol. If necessary, other options to lower cholesterol are available. For example, exercise and a low fat/high fiber diet may help. Also, other cholesterol-lowering drugs you may want to inquire about include niacin, cholestyramine, and gemfibrozil. While you have a complicated situation, your doctors can work together to help. Do not try to sort it out alone.

Q: I am at a total loss. I recently had an MRI that showed 17 lesions, but the neurologist said that the lesions were not big enough to be caused by MS. The research I have read states in many cases that you can't confirm MS right away.

Additionally, the person reading the MRI at the imaging facility wrote in the script that it was MS.

I am still worried about what these lesions are and what they will become. I am going to have another MRI in six months to see if the lesions have changed. Can smaller lesions still be indicative of MS, or could these lesions be attributed to some other condition? Is there any other type of testing I may do to find out more about these lesions?

A: Multiple small lesions on the MRI are only one factor in determining the diagnosis of MS. Other conditions can look similar to MS on the MRI. Other factors in the diagnostic decision making include the neurological history and examination, the course of the illness, the presence of other previous conditions/diseases (such as previous head injury, high blood pressure, diabetes, or migraines), the spinal fluid evaluation, the location as well as size of the MRI lesions, the evoked response testing (especially the Visual Evoked Potentials), and blood tests to rule out a variety of other MS-mimicking diseases. You may not have heard of "evoked potential testing," since it is not used that often. They are done when diagnostic questions arise. Evoked potential tests measure the speed of nerve conduction within the central nervous system from the eyes, ears, and limbs.

The radiologist who interprets the MRI sometimes does not have access to these other data. The first thing to do when there is a question is to have your neurologist talk with the radiologist. I suspect this has already happened. Most radiologists are not so bold as to make an "MS diagnosis" by the MRI. I suspect the report merely said that MS was one possibility.

If there are questions remaining, I usually recommend the additional tests (just mentioned) and a repeat MRI in three to six months before arriving at any conclusions. While I usually recommend early treatment (noted on page 18), I do not treat until the diagnosis of MS is reasonably assured. Your diagnosis does not seem to be firm. Last, you could get a second opinion from an expert at an MS center.

Q: I was diagnosed in late 1993 with relapsing-remitting MS at the age of 36. I am now 51, and in the past year, I have graduated to the secondary-progressive stage. It has greatly affected my left side with weakness and pain. I ambulate with a walker and use a wheelchair for those times for long distances. I take Baclofen, Dantrolene, and Diazepam for spasticity. My therapies have included Betaseron, Copaxone, Tysabri, and I will soon undergo my second Novantrone treatment.

My question to you is: what are your feelings regarding mercury in silver fillings? Everything I have read indicates no correlation between mercury and MS, however, I am seeing more and more internet blogs from people who have had these fillings removed and their MS symptoms literally disappear.

In my personal experience, a close friend

of my husband's was diagnosed with arthritis and was nearly wheelchair-bound from it. He had all his silver fillings removed and remains symptom-free to this day. At our local YMCA, I met a man in his mid-50s who explained that he was diagnosed with MS almost 30 years ago after frequent falls. A few years later he had all the silver fillings in his mouth removed, and has been completely symptom-free ever since and his doctor states there is no sign of MS on his MRI.

I have discussed this with my dentist. Obviously, he can't recommend that I have this done, but explained the procedure to me. I am planning to also discuss this with my neurologist, as I am seriously considering having my silver fillings removed. What are your thoughts on mercury and silver fillings in relation to MS?

A: You have been through a gamut of treatments. The good news is that I predict two new treatments may be available in this next year. They have different treatment actions than the current meds and may be worth considering when they are available. They also have different "adverse event" profiles, so your doctor will need to help you put things together.

As for the removal of mercury fillings, this metal has been blamed for many diseases, even though no scientific data exists to support these claims. True mercury toxicity

has different signs and symptoms than MS. Nonetheless, the "Mercury causes MS" theory has been around for years. I have had many patients go through the removal of teeth fillings. Many feel better for awhile having done the procedure, but their disease usually continues to progress.

You mention the miraculously cured patients, and I am pleased for them. In my experience, some patients (10-15 percent) have a "benign form" of MS, where they get very sick but recover and continue to do well, without any treatments. Unfortunately, some of these patients get more disability later in life.

The relapsing-remitting form of MS is very tricky when judging treatments, which is why rigorous, placebo-controlled, blinded studies are necessary to accurately evaluate a potential therapy. Remissions occur naturally. Determining a treatment effect requires a blinded comparison between the treatment and the placebo groups. In MS trials, improvement can be seen with the patients on placebo. However, this placebo effect is less than the treatment effect.

In summary, the current FDA-approved treatments have stood the test of time. I refer you to the answer on page 18, where you can read the reports of proven treatment successes after 15 years – in scientific clinical trials. Mercury removal has been around for a longer period of time, but there is no scientific data to show any long-term benefits. It is a lengthy procedure with no scientific data to support its benefit in MS. After you take the Novantrone, if it is not successful, talk to your doctor about the new, oral treatments which are likely to be coming soon. ◆

Jack Burks, MD is the chief medical officer for MSAA. He is an international MS neurologist, writer, lecturer, and researcher, who assists with the development of new MS therapies and advises patients, families, MS organizations, and healthcare groups. Dr. Burks is a member of the Clinical Advisory Board of the NMSS. He has written and edited three MS textbooks, as well as numerous chapters and articles on MS. In recent years, he has lectured and evaluated patients in more than 40 countries.

To Submit Questions...

Please submit your questions to:

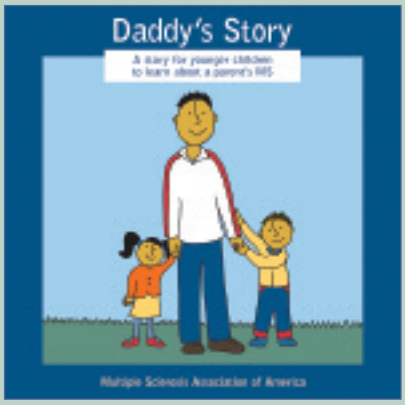
MSAA
Questions for Ask the Doctor
c/o Dr. Jack Burks
706 Haddonfield Road
Cherry Hill, New Jersey 08002

Readers may also send in questions via email to **agriese@msassociation.org.** Please be sure to write "Ask the Doctor" in the subject line.

Please note that MSAA is temporarily reducing the number of issues of *The Motivator* due to budget reductions. For the upcoming fiscal year (7/1/2010 through 6/30/2011), MSAA will publish a Summer/Fall 2010 issue in late September, and a Winter/Spring 2011 issue in late March.

NEW PUBLICATIONS *from MSAA*

Daddy's Story

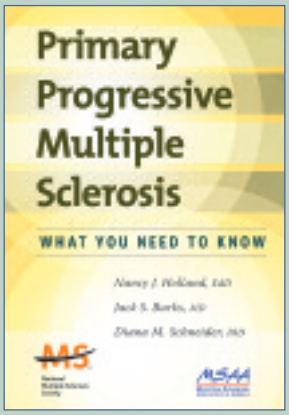


This new book is written and designed for children who are 3 to 7 years of age. Its purpose is to help children understand MS and to reduce feelings of anxiety and worry. Much of the book focuses on the symptoms that a parent may be experiencing when diagnosed with MS. It also addresses various details about the disease, including the issues of taking medication and possibly going to the hospital. The overall theme of the book is both uplifting and loving, showing that daily life can go on as "normal" with some adjustments. *Daddy's Story* has been directly modeled after MSAA's *Mommy's Story*, winner of four publication awards including a Grand APEX Award in 2007.

This book may be ordered free of charge at **msassociation.org/publications**. Individuals without internet access may call MSAA at **(800) 532-7667** to request a copy.

Primary Progressive Multiple Sclerosis: What You Need to Know

By Nancy J. Holland, EdD; Jack S. Burks, MD; and Diana M. Schneider, PhD



Created as a joint project between the Multiple Sclerosis Association of America and the National Multiple Sclerosis Society, this book is dedicated entirely to the primary-progressive multiple sclerosis (PPMS) population. Written by top experts in the field, initial chapters address how PPMS differs from other types of MS, how it is diagnosed, and ongoing research into possible treatments for this form of the disease. Later chapters provide detailed explanations on topics such as: the benefits of rehabilitation; symptom management treatment options; technology and adaptations; maintaining wellness; emotional and quality of life issues; family and social issues; care partner support; and economic issues. A glossary and an extensive resource listing are included. This is a valuable and informative publication for everyone in the PPMS community.

This book may be ordered free of charge at **msassociation.org/PPMS**. Individuals without internet access may call MSAA at **(800) 532-7667** to request a copy. Copies are limited, so this book may also be borrowed from MSAA's Lending Library when free copies are no longer available. Please see page 48 for more information on the Lending Library.

Research News

Written by Jack Burks, MD
and Susan Wells Courtney

Ampyra™ Approved to Improve Walking for Individuals with MS

On January 22, 2010, the United States' Food and Drug Administration (FDA) approved Ampyra™ (dalfampridine), to improve walking in individuals with MS. Ampyra is an oral, timed-release medication developed to improve the conduction of impulses between damaged nerves of the central nervous system (CNS). Phase III clinical trials showed that a greater number of individuals with MS experienced improvement in walking speed when taking Ampyra, compared to when taking a placebo.

Ampyra (pronounced "am-PEER-ah") was developed by Acorda Therapeutics and is manufactured by Elan Corporation. Formerly known as Fampridine-SR, Ampyra is a sustained-release version of 4-aminopyridine (4AP). In earlier studies, larger doses of the drug were given and the risk of seizures became a concern. Given in timed-release tablets, the risk of seizures did not differ from the placebo group.

MSAA Chief Medical Officer Jack Burks, MD notes, "The majority of my patients experience problems with mobility, so this approval comes as welcomed news to the entire MS community, especially since it has shown positive results with both relapsing and progressive forms of MS.

"Following the instructions for correct dosing is absolutely essential. Taking more than one tablet within 12 hours, or crushing or splitting a tablet, will increase the risk for seizures. Some patients tend to think that taking more of a symptom-management drug will result in greater effectiveness, but this is definitely not the case with this type of medication. I strongly advise patients not to exceed the recommended dosing."

Individuals with a history or evidence of seizures, or with moderate to severe kidney problems, should not be given Ampyra. Kidney function is important, since nearly all of this medication is removed from the body through the kidneys. If the kidneys are not functioning properly, levels of the drug will rise and increase the risk for seizures.

Ampyra is a symptom-management drug to improve walking in MS patients. It may be given in conjunction with any FDA-approved disease-modifying therapy and with other

ALSO IN THIS SECTION:

symptom-management drugs, but patients need to check with their doctor before combining Ampyra with other medications.

According to the FDA, the most common side effects reported for Ampyra include urinary tract infection, insomnia, dizziness, headache, nausea, weakness, back pain, balance disorder, swelling in the nose or throat, constipation, diarrhea, indigestion, throat pain, and burning, tingling, or itching of skin.

Anyone interested in this drug for symptom management should consult his or her physician, who can help to determine if this drug is appropriate. It is distributed exclusively through a network of specialty pharmacies, coordinated by Ampyra Patient Support Services. Consumers as well as healthcare professionals may contact Ampyra Patient Support Services at **(888) 881-1918** or visit **www.ampyra.com** for more information.

For a more detailed version of this article, please refer to MSAA's online version, which may be accessed by visiting **www.msassociation.org** and then selecting "Recent News." To request a printed copy of the online article, or to speak with one of MSAA's Helpline consultants, please call (800) 532-7667. ◆

FDA Approves Botox® for Upper Extremity Spasticity

On March 9, 2010, the United States' Food and Drug Administration (FDA) approved Botox® (onabotulinumtoxin A) for the treatment of spasticity in the flexor muscles of the elbow, wrist, and fingers in adults. Manufactured by Allergan, Inc., this drug is administered via injection by a medical professional and is available through prescription only. The approval includes its use for individuals with MS.

Spasticity or muscle stiffness and tightness is experienced by many people with multiple sclerosis (MS), stroke, brain injury, or other neurological conditions. Spasticity can severely limit the use of one's arms and hands as well as produce pain.

Botox is given by an injection directly into the affected muscles. It blocks conduction between nerves and muscles which temporarily paralyzes spastic muscles, usually for a few months. This drug was first approved 20 years ago by the FDA for the treatment of certain eye-muscle disorders. Since that time it has also been approved by the FDA to treat three other disorders, which include a condition causing abnormal head position and neck pain; symptoms of severe underarm sweating; and the cosmetic use of temporarily improving the appearance of severe frown lines between the eyebrows.

The risks and benefits associated with Botox should be discussed with one's doctor. The most common side effects include nausea, fatigue, bronchitis, pain, and muscle weakness. Breathing and swallowing difficulties have been reported.

Botox injections add another treatment to the growing list of medications that may help

MS symptoms. Botox is a symptomatic treatment only and is not a disease-modifying therapy for MS, so it should not be used as a substitute for these therapies. The FDA points out that Botox "is not intended to substitute for physical therapy or other rehabilitative care." Individuals who may benefit from this treatment for spasticity in the elbow, wrist, and fingers should consult their physician for specific recommendations.

For additional product information, readers may visit **www.allergan.com** or call Allergan's Customer Service at **(800) 433-8871**. For a more detailed version of this article, please refer to MSAA's online version, which may be accessed by visiting **www.msassociation.org** and then selecting "Recent News." To request a printed copy of the online article, or to speak with one of MSAA's Helpline consultants, please call **(800) 532-7667**. ◆

Chronic Cerebrospinal Venous Insufficiency (CCSVI) and Multiple Sclerosis (MS)

A great deal of media attention has been given recently to the possible connection between chronic cerebrospinal venous insufficiency (CCSVI) and multiple sclerosis (MS). CCSVI is a complex condition involving changes in blood flow from the brain back to the heart, which some researchers theorize could possibly lead to activation of the immune system, excess iron deposits, loss of myelin, and other nervous system damage.

Please note that all of these findings should still be considered preliminary at this time. Further studies are needed to confirm the theories proposed in this article.

Altered Blood Flow and Its Potential Effects

With CCSVI, the veins located on the outside of the brain (extracranial cerebrospinal veins) – those designed to transport blood from the brain back to the heart – collapse and/or become blocked, a condition known as "stenosis." As a result, blood leaving the brain must be rerouted through smaller vessels around these primary veins, referred to as "substitute circles." These ancillary veins, however, cannot transport the blood as quickly or efficiently as those larger ones designed for this purpose. Not only does the blood flow slow down, but the blood may also flow backwards (referred to as "reflux"), and studies suggest that both the reflux of blood as well as a pulsing (back and forth) flow may be much more common in MS patients versus controls.

Studies have shown that when the normal blood flow is altered, especially when the flow of blood is reversed, the body may react with an inflammatory response. Of particular importance is the activation of surface adhesion molecules, which enable damaging immune-system cells (such as macrophages and T cells) to cross the blood-brain barrier, infiltrate the central nervous system (consisting of the brain and spinal cord), and potentially injure brain tissue, myelin (the protective covering of

the nerves), and nerve cells.

The proposed damage from CCSVI also involves an iron overload for individuals with MS. As with certain other neurodegenerative conditions, unusually high levels of iron may be present. Iron levels may be particularly high in the brain and spinal cord of individuals with MS. With CCSVI, where blood flow out of the brain is slowed down and even reversed, extra iron is believed to be deposited and stored in sites near these vessels.

How Iron Affects the Body

Iron is needed by all living things. In addition to maintaining cellular balance and enabling nerve cells to perform routine functions, iron forms tissues and blood vessels; it transports oxygen through the body via blood circulation; it enables nerve impulses to be transmitted; and is essential to the development of myelin and oligodendrocytes (which produce and maintain healthy myelin). Iron is deposited in varying amounts to the different cells within the body, according to their specific need for proper functioning.

While the benefits of iron in normal levels are clear – and critical for bodily function – conversely, too much stored iron can cause problems. For instance, as people age, iron is more likely to accumulate in the brain. Conditions such as Alzheimer's disease and Parkinson's disease can occur in connection with iron stores. The processes associated with excess iron in

the body are very complex, but it has been characterized as, "...one of the most dangerous catalytic elements responsible for the neurodegenerative process." (Levenson and Tassabehji, 2004)

Since the first description of MS by Charcot in the mid-1800s, MS lesions have been known to be "venocentric," or occurring around blood vessels. More recent studies have also shown that with MS, iron stores may be found constantly encircling venous walls. Additionally, iron overload is found in MS lesions, although this is a feature also observed with other neurodegenerative diseases. Excessive iron may occur as a result (versus a cause) of MS damage.

Please note that individuals should not reduce their iron intake unless recommended by their physician. Iron deficiencies can cause serious complications.

An Experimental Treatment Trial with Endovascular Widening of Narrowed and Blocked Veins

A leader in the current CCSVI research is Paolo Zamboni, MD, director of the Vascular Diseases Center at the University of Ferrara in Milan, Italy. He and others have been studying blood flow, inflammation, and iron stores in MS for several years. The results of Dr. Zamboni's pilot study in Italy were presented at the 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) held in September 2009.

More recently, Zamboni and colleagues have published their treatment data of 65 MS patients who underwent an angioplasty type of experimental procedure to potentially improve blood flow from the brain to the heart.

The Procedure

With CCSVI, reduced blood flow is seen in the internal jugular (IJV) veins and the azygous (AZY) veins. Reduced blood flow is observed in these veins to varying degrees in the head, neck, and spinal cord. This condition requires a combination of veins to be collapsed. According to the study results presented in the December 2009 issue of the *Journal of Vascular Surgery*, "CCSVI is strongly associated with multiple sclerosis."

An experimental endovascular procedure was used to widen the narrowed or blocked veins in a study of 65 MS patients (endovascular is defined as "within a blood vessel"). Lead investigator Dr. Zamboni refers to this as the "liberation procedure." One of the purposes of this study was to evaluate the safety and clinical outcome of this procedure in the treatment of CCSVI with MS.

The 65 participants included 35 individuals with relapsing-remitting MS (RRMS), 20 with secondary-progressive MS (SPMS), and 10 with primary-progressive MS (PPMS). A number of criteria were used to select the patients, including a confirmed diagnosis of MS as well as CCSVI, and normal kidney function. In addition, RRMS patients must have been taking FDA-approved disease-modifying treatments.

In this study, percutaneous transluminal angioplasty (PTA) was performed on the 65 MS patients by using a tiny balloon inserted

into an affected vein. The veins were accessed from a remote location in the groin, and the balloon was threaded through a vein until reaching the affected areas. The balloon was first inflated, held for 30 to 60 seconds, and then deflated. This process was repeated several times in each affected vein before the balloon was removed.

The procedure was done as day surgery using a local anesthetic, and patients were released after four hours of postoperative observation. Other physicians at other institutions have used stents to open collapsed veins. These patients were given a preventative dose of a blood thinner for three weeks following the procedure to reduce the risk of blood clots.

Safety and Vascular Study Results

According to Dr. Zamboni, the procedure was well tolerated, with no serious operative or postoperative complications. Six of the 65 patients reported postoperative headache that was temporary and went away on its own.

A major issue in the months following the procedure was that restenosis (where veins narrowed again) occurred in the IJV vein of 47 percent of the patients treated for IJV stenosis. This disappointing outcome occurred in the IJVs 16-times more frequently than in the AZY, and most often occurred at the eight-to-nine-month point following the procedure. Researchers state that a stent might be a logical solution, although dedicated devices of the correct size for IJVs are not readily available at this time. Technical improvements would be needed in the future.

Four patterns of stenosis were observed, and researchers note that certain patterns appeared to be associated with the different types of MS. According to the published results, in 90 percent of the PPMS patients (9 of the 10), the stenoses were limited to the veins which drain blood from the spinal cord. The reduced blood flow in the spinal cord, which occurred in several locations, may explain why the patients with PPMS experienced less benefit from the procedure than those with RRMS.

Neurologic Study Results

According to the published report, RRMS patients showed a "highly statistical improvement at 18 months" on the Multiple Sclerosis Functional Composite (MSFC), which measures leg and arm function, ambulation, dexterity, and cognitive function. Progressive patients (individuals with SPMS and PPMS), showed a "significant but limited improvement" at six months, but no improvement with respect to baseline at 18 months.

With regards to relapses in RRMS patients, 27 percent of these individuals were relapse-free during the year prior to the endovascular procedure. Postoperatively, 50 percent of the individuals with RRMS were relapse-free as of the 18-month follow-up time, which is a significant increase in the number of patients who did not experience a relapse.

However, the lack of an MS control group limits interpretation, since many MS trials have shown that the placebo-treated group may also improve in certain outcomes. The practice effect of repeated

testing may have influenced the positive MSFC outcomes as well.

All of the RRMS patients whose veins remained open were relapse-free following the procedure. However, the numbers are small and the overall annual relapse rate (ARR) for the entire RRMS group was not significantly affected, since this included those RRMS patients who had a restenosis of the IJVs.

In terms of MRI results, the percentage of patients with active gadolinium-enhanced lesions at MRI was significantly reduced from 50 percent to 12 percent. However, the authors note that different MRI equipment was used, and this lack of consistency could have an effect on the actual outcome. Also, without an MS control group, "regression to the mean" may be a partial explanation for improvement. (This means that patients with active lesions on an MRI are more likely to have less MRI lesions on subsequent studies, even without therapy.)

Interpretation of Study Results from MSAA's Chief Medical Officer

MSAA Chief Medical Officer Jack Burks, MD, points out the value of putting forth a new hypothesis such as this, which is both creative and encouraging. He also explains that "thinking out of the box" may be needed to develop future treatments. Dr. Burks adds, "Finding interesting data to support this hypothesis is intriguing. These mixed results in a small pilot study are not surprising and may lead to more precise findings in larger, scientific trials in the future.

"Over the past century, more than 100 proposed treatments for MS have reached this stage of development," Dr. Burks continues. "From here, scientifically valid, multi-center studies are needed to demonstrate efficacy without significant adverse effects. The CCSVI scientists recognize the need for these additional studies and are not recommending this procedure, except as part of future clinical trials. For example, researchers need to agree on the most sensitive and accurate diagnostic test."

Specifically, in an article from Medscape Medical News (dated December 3, 2009 and written by Susan Jeffrey), Dr. Zamboni emphasizes that "...the current report should be viewed as an interesting finding that urgently requires replication by other groups."

Dr. Burks explains, "Dr. Zamboni is not advising patients to rush out and have this procedure. I agree with his perspective. Additionally, in non-experienced hands, surgery may not be as safe as demonstrated by Dr. Zamboni. Changes in the surgical approach may be forthcoming (such as stents versus balloon catheterization). Future trial results may be better, with fewer incidences of restenosis.

"This procedure cannot be considered a proven treatement at this time. Fifty percent of RRMS patients still had relapses after surgery. In addition, all RRMS patients were on DMTs. The specific relationship to relapses and restenosis is important. The researchers are planning the right steps. However, the results from future studies are needed before relevant conclusions and recommendations can be established."

The CTEVD Study by the University at Buffalo

As a follow-up to the small, pilot study conducted in Italy by Dr. Zamboni, a larger study is now underway. Titled, "Combined Transcranial and Extracranial Venous Doppler (CTEVD) Evaluation in MS and related Diseases," this larger study is being conducted at the University at Buffalo in New York.

According to the University, "The main goal of the CTEVD study is to investigate the prevalence (frequency) of CCSVI in patients with multiple sclerosis (MS) when compared to healthy controls (HC) and controls with other neurological disorders (OND). Another important aim of the CTEVD study is to investigate the relationship between CCSVI and clinical, magnetic resonance imaging (MRI), and environmental-genetic outcomes in MS patients, HC, and controls with OND."

In February 2010, researchers from the University at Buffalo reported preliminary results from the initial phase of this study. Based on the first 500 participants, more than 55 percent of the individuals with MS were found to have CCSVI. Less than half as many healthy controls were found to have this blood-flow abnormality.

On March 12, 2010, the University at Buffalo gave an update on the CTEVD study. The program has been modified as advised by the University's Institutional Review Board. According to the update, "The purpose of the program modification was to ensure that individual study results were not proffered by BNAC as a diagnosis for which any treatment is implied or advised." The report also notes that at this time, funds are not available to support the study and participants will need to pay their own fees for tests ($4,500 per person).

For more information, readers may go to **www.buffalo.edu/news/10937** to view the February press release from the University of Buffalo. Readers may also go to **www.bnac.net/?page_id=517** for specific information on study enrollment at the University at Buffalo. Individuals without internet access may contact MSAA's Helpline consultants for assistance at **(800) 532-7667**.

Closing Notes

Dr. Burks concludes, "To date the data establish an association, but do not yet establish a causal relationship of CCSVI and

MS. Fortunately, research funding is rapidly becoming available to answer some of the important questions regarding the potential causal link. Also, researchers are working to better determine the most accurate diagnostic tests as well as the most effective and safest procedural approaches for correcting the situation.

"What is the status of the current treatments for CCSVI? Two approaches have been tried. Venous angioplasty is done by placing a catheter into the 'closed' veins to 'open' them up. However, this current procedure may not keep veins open for long, since almost 50 percent of some veins re-stenosed in less than a year in Dr. Zamboni's paper. Another potential corrective surgical procedure is placing stents in the veins to keep them open. However, these stents may break off, since the walls of veins may be very fragile. On one occasion, an emergency heart surgery was performed.

"Therefore, we still have more to learn before researchers establish the possible causal link as well as establish the best diagnostic tests and treatments. I wish them success in getting us these answers quickly.

"While the researchers work diligently to find answers, I recommend these procedures be focused in the research arena. The next steps are to better understand the causation issues, the proper diagnostic procedures, and the safest/most effective way to treat the abnormality. We are not there yet but the research is already underway. We need to let the science proceed as planned and to wish the researchers much success. MSAA will continue to provide balanced updates as the research work progresses. For now, your doctor is your best guide."

For a more detailed version of this article with resources, please refer to MSAA's online version, which may be accessed by visiting **www.msassociation.org** and then selecting "Recent News." To request a printed copy of the online article, or to speak with one of MSAA's Helpline consultants, please call **(800) 532-7667**. ◆

Positive Study Results with Oral FTY720 Leads to Granting of Priority Review Status by FDA

In January 2010, the results from two large Phase III trials with oral FTY720 (fingolimod) were published in *The New England Journal of Medicine*. According to a press release from Novartis Pharmaceuticals Corporation (makers of FTY720), the TRANSFORMS and FREEDOMS studies showed positive results in reducing relapses, disability progression, and MRI lesions when MS patients were given FTY720.

TRANSFORMS was a one-year study with 1,292 individuals with MS. Participants were given either FTY720 or interferon beta-1a (Avonex®). FREEDOMS was a two-year study with 1,272 MS patients. This latter study compared FTY720 with a

placebo. Two dose levels were used in both studies (0.5 mg and 1.25 mg). Given the best benefit-risk profile, Novartis will be seeking FDA (and European) approval for the smaller dose of 0.5 mg taken once daily.

In the lower-dose group of the one and two-year studies, relapses were reduced by 52 percent and 54 percent, respectively. Also in both studies, the lower dose reduced the risk of disability progression, as well as reduced brain lesion activity and brain volume loss, as measured by magnetic resonance imaging (MRI).

In February 2010, Novartis announced that FTY720, now given the new brand name of Gilenia®, had been granted priority review status by the FDA. This designation reduces the FDA's review process from 10 months down to six months. The drug was submitted for review in December 2009, so a decision on the approval of FTY720 could come as early as June 2010.

Such a decision would make FTY720 the first approved disease-modifying therapy taken orally (by mouth) for the treatment of MS. However, Novartis cautions that this investigational drug contains an ingredient which has not been approved before (a "New Molecular Entity"), and this may require an extension of the review process beyond the anticipated June 2010 deadline.

FTY720 is from a new class of drugs referred to as "sphingosine 1-phosphate (S1P) receptor modulators." It works by preventing the release of certain lymphocytes (immune system cells) from the lymph nodes, so these damaging cells cannot reach the brain. According to Novartis, FTY720 reduces inflammation and may also have a beneficial effect on cells in the central nervous system (CNS).

The most commonly reported side effects from both the treated and control groups were inflammation of the nasal passages and upper part of the throat (nasopharyngitis), headache, and fatigue. Drug-related adverse events included: a reduction in heart rate (dose-related and transient); infrequent transient AV conduction block of the heart; a mild increase in blood pressure; macular edema (an eye condition that can affect vision, more common with the higher dose); and reversible elevation of liver enzymes. ◆

Phase 2 CHOICE Study Reports Positive Effects with Daclizumab

Biogen Idec and Facet Biotech Corporation, developers of daclizumab, report that when added to an interferon regimen, this drug reduces the number of new or enlarged MS lesions in patients with active, relapsing forms of MS. Additionally, daclizumab showed an increase in the number of a certain type of cell that helps to regulate the immune system. These results were published in the online edition of *The Lancet Neurology* and in the April 2010 issue of *The Lancet Neurology*.

The Phase 2 CHOICE study enrolled 230 patients with "active" relapsing MS (those having at least one relapse or one MS lesion during the past year while on interferon treatment), and who were currently taking an interferon treatment for at least six months prior to enrollment. Participants continued taking their interferon throughout the 24-week study and were given one of three add-on treatments: high-dose daclizumab every two weeks; low-dose daclizumab every four weeks; or placebo. The daclizumab and placebo add-on treatments were administered via subcutaneous injection.

In the high-dose group receiving both daclizumab and interferon treatment, new or enlarged gadolinium contrast-enhancing lesions (those enhanced on MRI with a dye) were reduced by 72 percent, compared to those taking interferon alone. The low-dose group experienced a 25-percent reduction. Daclizumab also resulted in a significant increase (seven-to-eight times the amount) in one type of "natural killer" (or NK) cells, which help to regulate the immune system and are associated with a decrease in disease activity.

Daclizumab is a humanized monoclonal antibody that binds to CD25. This is a receptor that is expressed at high levels on certain immune system cells (non-resting T cells) which may be activated with MS. This experimental treatment is thought to work by selectively targeting immune-system cells which play an important role in the MS process, without depleting "healthy" immune cells needed to help protect against other infections or illnesses.

Common adverse events (or side effects) were similar for individuals taking daclizumab with interferon and those taking a placebo with interferon. The most frequent, more serious adverse events were infections, occurring in 7 percent of the treated patients and 3 percent of the placebo group. All of these infections were resolved with standard therapies.

The developers of daclizumab are conducting a Phase 2b SELECT trial to evaluate the effectiveness and safety of monthly subcutaneous injections of this drug as a single therapy versus a placebo (no other disease-modifying therapies would be given). A Phase 3 DECIDE trial is planned to begin in mid-2010. ◆

Continued Efficacy and Safety Seen with 15-Year Evaluation of Copaxone

In February 2010, Teva Pharmaceutical Industries Ltd. announced the publication of their data from 15 years of prospective and continuous evaluation of Copaxone®. The 15-year study findings appeared in the February 2010 issue of the journal, *Multiple Sclerosis*. Given the positive results, this study has been extended to 20 years, and is presently in its 19th year. Copaxone is given via daily subcutaneous injections and is approved for individuals with relapsing-remitting MS (RRMS).

In terms of efficacy, more than 80 percent of individuals with RRMS taking Copaxone for 15 years are still walking without assistance. (This group had a mean average of disease duration of 22 years.) Additionally, two-thirds of these patients have not transitioned to secondary-progressive MS (SPMS), a form of the disease that follows RRMS and is defined by a progressive worsening of symptoms, versus relapses and remissions.

The annual relapse rate was reduced by 78 percent, and more than half of the study participants are reported to have experienced either stable or improved rates of disability. Their rates were measured by the Kurtzke Expanded Disability Status Scale (EDSS). This standardized test gives scores from one to 10 to measure disability, largely in terms of mobility.

In regard to safety, local injection-site reactions and immediate (but transient) post-injection reactions are the most common adverse events with Copaxone. No infections, cancers, or other immune-mediated conditions have been reported.

MSAA Chief Medical Officer Dr. Jack Burks comments, "Once again, long-term Copaxone data has proven it to be very safe, tolerable, and effective in those patients who have remained on therapy for 15 years. The data that 80 percent of Copaxone patients remain able to walk without any aids, after having MS for an average of 22 years, is remarkable. This report should encourage all patients to keep on medications for the long run. This data along with other long-term data, show how much the current medications have helped so many patients." ◆

VOLUNTEER YOUR TIME

Your time is valuable to MSAA! You can help people living with MS through a number of volunteer opportunities:

- *Host a fundraising event, including Swim for MS™, bake sales, dinners, or other events*
- *Serve as an MSAA Public Education Ambassador*
- *Help with patient education programs in your area*
- *Become an MSAA Resource Detective™*

For more information, visit ***support.msassociation.org/volunteer****, email* ***volunteer@msassociation.org****, or call* ***(800) 532-7667, extension 8****.*

Program Notes

Live Webcasts on Mobility and MS

Register for Live Mobility Webcast and Watch Earlier Webcasts On-Demand

Adding to our two dozen on-demand educational videos, MSAA has also produced a four-part live video webcast series titled *Staying One Step Ahead*. Made possible through the generous support of Acorda Therapeutics and Eli Lilly and Company, these interactive webcasts present important and timely information on the issue of mobility and multiple sclerosis.

The final installment of our series, ***Program Four – Energy Conservation and MS – for Home, Work and Travel*** **will broadcast live, Thursday, May 13, 2010, from 8 pm to 9 pm ET.** (For readers who do not attend the live webcast, the recorded webcast will continue to be available online.) This program will feature certified MS specialist and noted occupational therapist Jennifer Tamar Kalina, Director of Rehabilitation at the Comprehensive Multiple Sclerosis (MS) Care Center, at the New York University's Hospital for Joint Diseases in New York City. You may register at **www.msassociation.org**.

As mentioned, this webcast series features four programs on key aspects of mobility and MS. At the time of this article, Programs One through Three were recorded and archived as on-demand videos.

MSAA'S "Staying One Step Ahead – Program Two: Exercise and MS" webcast

In Program One, *Communicating Issues of Mobility to Your Healthcare Team, Care Partner and Family*, occupational therapist Dr. Kathleen Zackowski covers a wide range of information and provides practical advice and solutions to help MS clients improve their mobility. A key component in this process is to obtain an evaluation by an occupational therapist (OT). In the program, when asked to explain the process of an OT evaluation, she states: "Occupational therapy is to better understand what your activities of daily living are and how to achieve them. So part of it needs to be a conversation between you and your therapist as to what's important. …Some occupational therapists focus on orthopedic issues, some are involved in work adjustments, and some will help make your home safer."

Dr. Zackowski continues her response by stating:

"The kind of things you can expect from an OT assessment is first an interview so you get to know that person and he or she can get to know your needs, and then use some standardized tests. There are MS tests which measure cognition, fine motor skills,

walking, hand function, and fatigue. The idea is to get a global view of what you are like. Our job is to write goals that you can reach in a reasonable amount of time. Goals are critical because your insurance company won't cover therapy if you're not making progress."

In Program Two, *Exercise and Multiple Sclerosis*, post rehabilitation specialist Brad Hamler discusses and demonstrates a variety of safe and effective exercises for MS. During the webcast, Hamler raises many key points and addresses common myths about exercising, including the famous notion of 'no pain, no gain.' In explaining how exercise is important for MS patients, he notes:

"Having people work to the point of exhaustion is not a good idea – for anybody. And obviously people with MS cannot work that way, but you don't have to and you don't need to. First thing you want to look at when strength training is you're going to increase your ability to maintain your balance. We talk about balance and flexibility of muscles. Strong muscles are supple and able to support their structure. …As muscles are able to contract you may find that they're working more efficiently, which can help with spasticity."

These two brief excerpts from Programs One and Two represent just a small portion of useful, practical information on mobility and multiple sclerosis. Program Three is on Walking and MS, and is now available.

To view these and other MSi programs in their entirety, please visit **www.msassociation.org**. Happy viewing! ◆

Cranial MRIs Available through MSAA's MRI Institute

As the number of people with inadequate health insurance or no insurance continues to grow, MSAA has expanded its ability to serve more people through its MRI Institute. This program works to secure vital MRI scans of the brain so doctors and their patients can monitor the ever-changing course of their MS.

With the generous support of EMD Serono, Inc. and Pfizer Inc, MSAA's MRI Institute will be able to serve an additional 300 new clients in 2010. If you and your doctor are having difficulty securing a cranial MRI because of finances or lack of adequate insurance coverage, and have not received assistance through MSAA for an MRI in the past two years, please call the MRI Institute at **(800) 532-7667, extension 120** or email **MRIInstitute@msassociation.org**.

Thoughts about Giving

By Bruce Makous

Your Time is Treasured

We are very grateful to everyone who generously contributes to MSAA! Your gifts help us to help people living with multiple sclerosis.

Some very involved supporters contribute not only funds but also their time as MSAA volunteers. They find opportunities to help us with our programs for people living with multiple sclerosis, whether it's by hosting a local fundraising event, serving as an MSAA ambassador, serving on the national Board of Directors, or becoming involved in a regional MSAA function.

The most popular forms of volunteer involvement have been through local fundraising events. One type of event that has really skyrocketed in popularity in recent years has been our Swim for MS™ fundraiser. Swimmers all across the country have been conducting events at their local pool facilities and recruiting sponsors for their efforts.

David Poskin from Kansas conducted a model Swim for MS™ campaign. Last summer, he pledged to swim 50 miles between July 1 and Labor Day. He achieved his goal and attracted gifts from 58 supporters! It was a great, successful fundraiser.

Friends and supporters nationwide have come up with many other creative concepts for events, including golf tournaments, bake sales, luncheons, dinners, and carnivals. Students hold car washes for MSAA and teachers have dress-down days. Many engaged couples have arranged to make contributions to MSAA in place of wedding favors at their receptions. (Please see the advertisement on the inside front cover of this issue of *The Motivator*.)

There are a number of types of volunteer opportunities in addition to fundraising events. Programs that invite your involvement include our Public Education Ambassadors, regional volunteers, Resource Detectives, President's Circle Advisory Council, and others. We are looking for volunteers who want to help MSAA achieve its mission, by raising funds and awareness. If you would like to become more involved with MSAA, please contact Malcolm Friend at **(800) 532-7667**, **extension 117**, or go to **support.msassociation.org/volunteer** and register your interest.

This type of assistance helps MSAA deliver its programs and services that enrich the quality of life for everyone living with MS. For your enthusiastic involvement as a volunteer, we are extremely grateful. ◆

If you have thoughts about giving, please feel free to contact Neal Zoren at (800) 532-7667, extension 128, or email nzoren@msassociation.org.

Please help us continue to offer our magazine, ***The Motivator****, to the MS community. Your valuable contributions will help us with production and mailing costs. For more information, please contact Neal Zoren at the number above. Thank you for your support!*

MSAA Volunteers Make a Splash by Organizing Swim Fundraisers

Natalie Domeisen of Pittsburgh, Pennsylvania, organized a swim fundraiser with more than 50 of her friends participating.

David Poskin of Lenexa, Kansas, has raised over $3,500 for MSAA through his swim fundraiser.

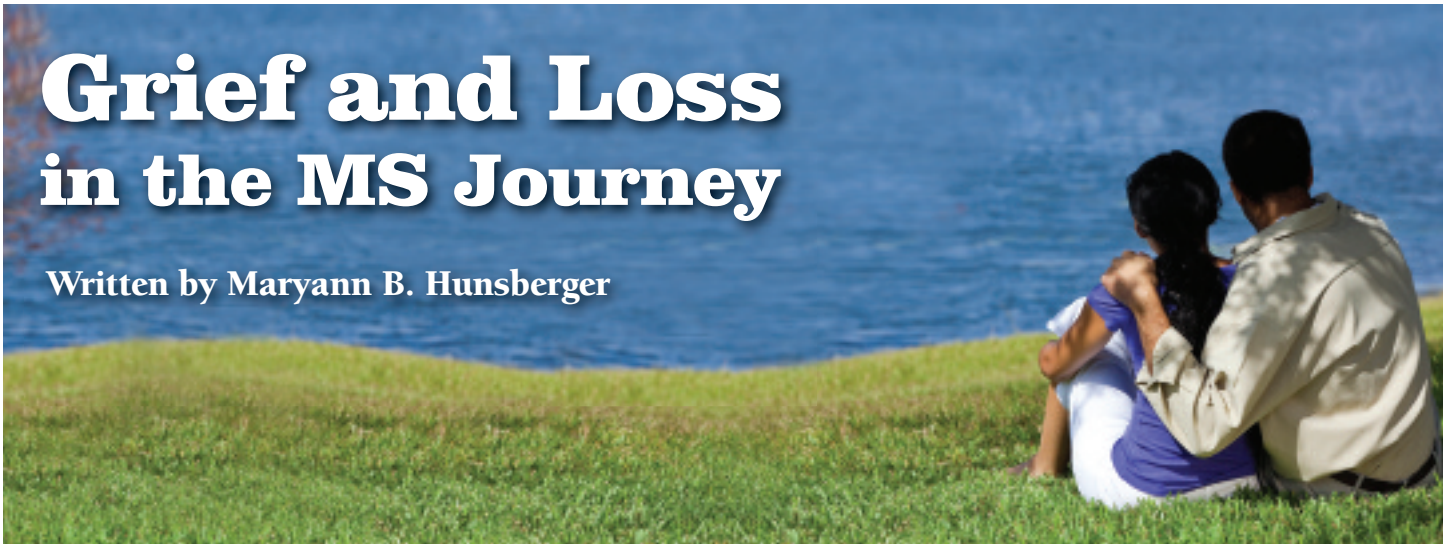
President's Circle Reception at Madame Tussaud's in New York

On January 29, 2010, MSAA hosted a President's Circle recognition event at Madame Tussaud's Wax Museum in New York City to honor our many supporters in the area. This provided a wonderful opportunity to acknowledge the individuals who have been helping MSAA through their volunteer efforts, as well as our generous financial supporters.

Romance and mystery novelist Laura Bradford (pictured above, right) of Mohegan Lake, New York, diagnosed in 2007, delivers remarks at the President's Circle Reception in New York. In her talk, Laura shared her thoughts about major watershed moments in life, including the moment when you hear the words, "You have MS."

In the photo at left, President's Circle Chair Ross Maclean (left) and Board Chair Eric Simons thank Kelly Donovan of Brooklyn for serving as a Public Education Ambassador in the area. ◆

Grief and Loss in the MS Journey



Written by Maryann B. Hunsberger

Four months into my disability, an able-bodied neighbor told me I should "get over" not being able to walk. She told me she knew exactly what I was going through because she was running the family business instead of living her dream of hoofing in the chorus line at Radio City Music Hall. As I sat in my wheelchair wondering who would walk my child home from school, buy groceries or cook dinner for my family, I felt that no one on earth knew how to show support for a newly disabled person who is grieving her losses.

Lara Krawchuk, MSW, LCSW, MPH, a clinical social worker in West Chester, Pennsylvania, says it's common for people in our culture to make grieving individuals feel uncomfortable. "Disability is an ambiguous loss, which makes it trickier. The losses aren't always obvious. If someone is still working, still has a family, or is still alive, people tell them to be grateful for what they have instead of supporting them. People try to force a happy face on them when they aren't ready for it, because ours is a very grief-phobic culture. Nobody can tell someone how to grieve or how long to grieve."

Krawchuk, a professor at the University of Pennsylvania who teaches clinical social work practice and a class on loss through the life cycle, has worked with many MS patients. She says that when MS patients lose the ability to physically function as they used to, others frequently fail to acknowledge that loss. "Grief is often under-recognized, unrecognized, or devalued. If nobody calls your loss a loss, you don't call it a loss. You don't have words for your grief and you don't have a way to make sense of what all of these losses mean to you."

Krawchuk says that loss often begins for the MS patient even before diagnosis. "From the minute that MS patients feel something is wrong with their body, even when they can't pinpoint what it is, losses start to pile up. They lose trust in their own bodies and in the belief that their bodies will take care of them if they take care of their bodies. They can lose

trust in people to support them. The long wait for a diagnosis causes some patients to lose trust in the medical system. Finally, the tricky nature of the disease makes people lose faith in themselves. They think they are losing their minds because they don't know what is wrong with them."

A New Way of Looking at Grief and Loss: Our Experiences Are Unique to Us

Elizabeth Kubler-Ross introduced the theory of the Five Stages of Grief when she published *On Death and Dying* in 1969. She identified the stages as denial, anger, bargaining, depression, and acceptance. In the past ten years, thinking has shifted away from this model.

Krawchuk explains, "Because of this theory, people think they are supposed to go through stages, but that doesn't fit with chronic grief, such as a chronic sorrow that may reshape and change throughout your life. The stages don't work for that. The new wave for grief theory is not about stages but about figuring out what grief and loss mean to the individual. It's more of a process than a destination or a goal. It's a lot messier, but it's a lot more real."

Since grief has unique features for each individual, it's important to recognize that all feelings of grief are valid. "One person with a new diagnosis might be angry, while another might be sad and another might be shocked. There is no one right way to grieve. Common emotions are sadness, sorrow, anger, guilt, regret, and frustration. I have counseled people who think they are crazy because they experience varying emotions, but I tell them that any emotion – except for wanting to harm themselves or someone else – is acceptable. It's imperative to have someone help you get through intense emotions, because it's too hard to do alone."

"Nobody can tell someone how to grieve or how long to grieve."

— Lara Krawchuk, clinical social worker

Krawchuk has counseled many patients who don't even realize they are grieving. "I will list their losses and ask if they have ever thought that they might be grieving because their relationships have changed, their health has changed, or their job has been lost. The loss of hopes and dreams are the hardest thing, because family members are usually afraid of these same things."

Complications can arise when family members and patients experience grief in different ways. Since our experiences are unique to us, nobody else can fully understand what we are going through. Nor can we fully understand someone else's grief. "One person in a family might go through one emotion while grieving, but their loved one might experience grief differently. They are on the same roller coaster and can't get off. But, one is in the front car and the other is in the middle or back car. Although the ride is

the same, the experience is different. They can't understand why the other person isn't reacting like they are. This can make people unable to support each other. Therapists try to help people to bridge the gap between their experiences, helping people navigate and find strengths, commonalities, and differences."

Sudden Temporary Upsurges in Grief

Even Kubler-Ross eventually acknowledged that the stages weren't meant to be seen as a ladder with a final destination, and that people may skip stages or go back and forth. Krawchuk continues, "There is no right visible path, no ladder with acceptance being the finish line. The goal is to feel less distress, but the race can be run over and over again. Since MS is chronic, it makes sense that the grief will also be chronic when recurrences happen. But with these recurrences, the grief usually won't have the same intensity."

Grief author Therese Rando called these episodes "Sudden Temporary Upsurges in Grief." Krawchuk notes, "MS patients can have these upsurges forever as their illness changes or as they bump up against something else they can't do. Realize that this is perfectly normal and acceptable. Don't let anyone tell you that you are flawed for having these grief surges."

Krawchuk says something positive can come out of these upsurges. "It makes no sense that you accept something once and you are done with it, because the disease is always present. When a patient thinks he or she has accepted the situation, but has an upsurge in grief, that doesn't mean the person is weak or hasn't been handling their situation well. It just means that this is typical of MS. Sometimes, you need to work things through again. In fact, with each flare-up, patients might learn to make more sense out of what is happening to them. This awareness can be part of the process of lessening grief."

The Path to Lessening Grief

Many MS patients may be sad and hurting about their diagnosis, but the pain does lessen for most people with time and effort. "People should feel empowered to speak up if they are suffering. For many people, healing comes from telling their story, whether telling loved ones or outsiders who can provide support without their own needs clouding the issue. Some people need to tell their story repeatedly as their illness changes. Speaking at groups, calling hotlines, talking to therapists, and talking to a person's health team can be helpful. Voicing one's feelings can empower patients to know that it's okay to need what they need."

Perhaps the most important aspect in dealing with grief is to recognize who is supportive and who is not. "Figure out who is helpful to you and overtly reach out to those people. That's critical. Just because someone is well meaning, doesn't mean he or she can help. You are the boss who decides who is helpful. If patients can't think of anyone who supports them in a way that feels good to them, they need to figure out where they can get that support. It doesn't matter where you find support. If an internet chat room helps more

CONNECTING WITH GRIEF

MSAA's Life Coach Anne Marie Buck, MS, states that when grieving the losses that MS can cause, several steps can be helpful.

- **Remember to be kind to self.** "Listen to what you are thinking. If you are being judgmental or critical, substitute compassion and say to yourself what you would say to a good friend who is grieving. Healing takes place with nurturing and kindness."
- **Look for ways to reduce losses.** One of Buck's clients stopped leaving the house when she could no longer walk. Eventually, she transitioned to a scooter and could go to restaurants or watch her children play sports. "Opening up to new possibilities can help return to life the things that need not be lost."
- **Don't let fear of grief stop progress.** "Resisting our emotions can increase our discomfort, like holding a beach ball underwater. It takes a lot of energy, and ultimately, the ball will rise to the surface anyway. Think of grief as waves at the beach that come and go. Each wave has a crescendo and eventually disappears. Some waves are strong and some are mild. Make peace with that ebb and flow and realize that grief will come and go, as is true with all emotions."
- **Schedule time for grief.** "Make an appointment with grief. Picture the life you thought you'd have, and connect with the grief and loss you feel. Wrap yourself in a warm blanket like a big hug. Connect with your grief through music, poetry, novels, movies, or anything that can help you to commune with your grief."
- **Don't resist grief.** This can cause our bodies to tense, which brings tension into our lives. Therefore, Buck stresses paying attention to how the body feels when it's expressing grief. "Does your face flush? Do your eyes tear? Does your stomach wrench? Let that expression go forward. Don't resist it."
- **Express your grief.** Talk to a supportive person. Journaling or drawing can be useful, since some find it helpful to use the arts to communicate grief. "Expressing grief is an important facet in beginning to heal."
- **Use rituals.** Rituals can help express emotion and move people past a grief episode that is ending. "Take a journal, tie it with a black ribbon, and put it aside to show that this episode of grief has passed."

Buck says it can be helpful to realize that when the grief passes, it's not over forever. "Grief is part of life. Each wave of grief can help us be more resilient, wiser, and more prepared for the next wave. Start to picture the life you can actually have and take steps toward creating it."

than a professional or religious organization, recognize this."

The second most important aspect is figuring out what this experience means to and for the patient. "Patients need to find meaning when nothing makes sense. They ask, 'Who am I now?' and 'What will my future be?' The final source of support – and a good way to figure this out – comes from patients expressing themselves, whether through talking, journaling, doing art, writing, or any form of expression that helps them come up with a manageable solution. This helps to honor the MS experience."

Be Sure to Use Healthy Methods of Distraction

While some people prefer to talk or write about their experiences, some prefer to distract in other healthy ways. Krawchuk suggests the following examples of healthy distractions:

1. **Read a book**
2. **Laugh while watching a funny movie**
3. **Go swimming**
4. **Pray or meditate**

"These are all healthy ways to distract from the illness. Only the individual knows if what is going on is helpful. It's important to be open to trying different things."

Krawchuk identifies the top four unhealthy methods of distraction, which should be avoided if a patient wants to succeed in working through grief. The unhealthy methods are:

1. **Bottling up feelings.** "If there is pain and it feels like it needs a voice, don't stuff it in. Write it down, talk to a pastor or a rabbi, talk to a therapist. Otherwise, grief can turn into clinical depression, rage, or isolation from loved ones.
2. **Using drugs and alcohol.**
3. **Pushing away friends and family.**
4. **Ruminating on guilt.** "It's dangerous for patients to dwell on what they think they should have, would have, or could have done."

Recognize and Accept Your Own Style of Grieving

It's important for MS patients to understand their own method of grieving. "Some patients might need to take an hour a day, or one day a week, to feel the grief. It's a skill to learn how to take out the grief and put it away. Workbooks on managing anxiety and cognitive behavioral therapy can help a

Points to Remember

- MS involves losses and losses often need to be grieved.
- Grief is unique to every individual.
- Family members might not understand each other's grieving methods.
- Honor one's losses.
- Work through the pain and emotions with help and support.
- Be creative in how you define support and how you reach out for support.
- Don't let anyone tell you not to grieve or that you need to put on a happy face.

person to learn this skill. Mindfulness meditation – being with the suffering without judging it – is a wonderful skill for managing pain. And a therapist can be a patient's safe place to talk about his or her pain, thereby lessening the pain the rest of the week."

Krawchuk says people are enormously resilient beings who learn how to grow, thrive, and live well within the realities of their own experiences. "MS patients become good at knowing how to express themselves, how to seek advice and support, and to not take negative comments as their fault. You don't need to own every well meaning, but missing-the-mark, advice. I have seen people come through grief knowing much more about themselves."

Many of Krawchuk's patients have succeeded in working through and alleviating grief. Although the effort can be difficult, working through grief leaves room for pride and growth. "It's good to feel proud of getting up and going to work even when exhausted. A parent can be proud of getting the children to school on time. A care partner can be proud of supporting their partner. People can be proud of growing as human beings who don't let the small stuff drag them down. The takeaway message is to not do it alone and to not listen to people who tell you to put on a happy face. Denying grief is wrong and dangerous. These people might mean well, but they don't know what they are talking about. It's natural, normal, and acceptable to have grief when there is loss." ◆

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Living and Loving with MS

A loving memory, a spouse's experience, with MS

By Linda D. Britton

To all the husbands and wives whose journey has embarked on the challenges of multiple sclerosis in the one you love, hold on tight. But hold on. You are about to encounter the richest human experience you can imagine.

MS at the onset is very frightening for both the individual with MS as well as his or her spouse. It takes some time to adapt it into your life. Soon after my husband, John, was diagnosed, we read an article about MS. This was our first taste of what might come. It was very negative and terrified both my husband and me. Quickly, we gathered more information, and that helped.

Our "normal" became something different. Our lives, perfect as we thought they were, changed very quickly. If you have children, their lives change in an instant as well. Our children were quite young – Jamie and Josh were ages 5 and 4 at the time of John's diagnosis. At the onset of symptoms a few years earlier, Jamie was about 6 months and Josh was a bun in the oven. We wondered for several years what we were dealing with.

John and I got his diagnosis over the phone. I was concerned about John and the family, including the fact that John had a job which required travel. I talked to the doctor after John was finished and I asked, "What

The author, Linda Britton, with her husband John in their used bookstore.

am I supposed to do? We have two little kids." The doctor answered, "Keep your life as normal as possible." I thought at the time, "You just dropped a bomb on us, and you are suggesting normalcy." But over the years, I realized that this was the best advice I could have gotten.

To manage, grow, and maintain a healthy family with the presence of a serious chronic illness, is a monstrous challenge for everyone. We didn't tell the kids right away. They were young, and we had high hopes that John would be one of the lucky ones who wouldn't be greatly affected by MS.

Jamie was in first grade when the local MS organization was sponsoring an "MS Read–a-Thon." She got a lot of sponsors, obviously, because John had just been diagnosed. She

watched quietly while people with MS did presentations to her class. She felt so sorry for them, and she even won the prize for the most money raised.

Then our daughter overheard the babysitter tell the other kids, "Jamie won because her dad has MS." We hadn't yet told Jamie that her father had MS, and I felt that we were wrong to not tell her sooner. So, my personal advice is to tell the kids as soon as you know, whether you think they will understand or not – because they need to hear that from Mom and Dad, and not from the babysitter.

We spent our life with MS in constant adaptation. We were a team in everything we did. I'd work during the week, while John would shuttle the kids to school, and soccer, and dance. I don't think we ever missed one of their functions, and they were both very active kids.

I had a demanding job, so John helped me with things at home. He would pick up the dry cleaning, take something out of the freezer for supper, hang up the laundry, and do woodworking. Then a change came in our life, and we opened up a small, used and rare bookshop. John was brilliant, and the most well-read person I have ever known. We eventually took our little bookshop online, adapting once again.

Our weekends were jammed-packed with projects at home. We worked on cars, we laid linoleum and tile, we did anything that needed to be done around the house.

Later in his life, John was the brain, and I was his hands or legs. He would sit on a stool by the car, and have me remove this bolt, remove that part, or whatever, and we kept our cars running that way. When we were done, we would laugh and smooch… so proud of ourselves, that we saved that $500.

The spouse with MS has to work hard to make sure he or she is a pleasant and loving part of the family unit. And everyone else has to do the same. As the spouse of someone with MS, you will work harder than you ever imagined, handling your responsibilities, as well as those of others.

The key in my situation was that my husband was always loving, and always did absolutely as much as he was physically capable of doing. What that did, was to keep me in the role of wife, rather than caregiver, for many years. And it was through that experience, that we maintained our "normal."

Here's another thought I have for you. Put MS in the MS box. It is perfectly fine to be mad at MS. (I could think of a few choice words for it myself!) Love your spouse, hate the MS. In order to do that, I found that I needed to recognize when I was angry at MS. Many times I had to stop, take a breath, and realize I was mad at MS. When I did that, I was free to love my husband, as the person he was.

The richness that I mentioned above was incredible. Chronic illness causes one to dive deep into his or her spirit and character. It is contagious to the people around you. I watched my entire family grow to great depth, as we were challenged in this way.
We are better people for it. ◆

Spread the Word

Primary Progressive Multiple Sclerosis: What You Need to Know

Written by Nancy J. Holland, EdD; Jack S. Burks, MD; and Diana M. Schneider, PhD
Published by DiaMedica Publishing
MSAA Book #48

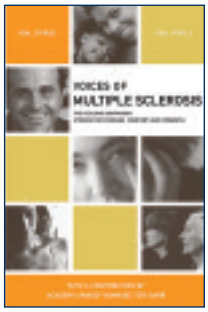
Written by top experts in the field, initial chapters address how PPMS differs from other types of MS, how it is diagnosed, and ongoing research into possible treatments. Later chapters discuss rehabilitation, symptom management, technology, and many factors for maintaining wellness. This book may be ordered free of charge by visiting **www.msassociation.org/PPMS**. Individuals without internet access may call MSAA at **(800) 532-7667** to request a copy. Copies are limited, so this book may also be borrowed from MSAA's Lending Library when free copies are no longer available.

29 Gifts: How a Month of Giving Can Change Your Life

Written by Cami Walker
Published by Brightside Communications Inc.
MSAA Book # 131

In this well-written and sensitive book, author Cami Walker talks about life with MS. Through the giving of "29 Gifts," she describes how she was able to look outside of herself and her own challenges. She finds that she can be helpful to others, and through this process, is able to achieve personal empowerment.

Voices of Multiple Sclerosis: The Healing Companion Stories for Courage, Comfort and Strength



Edited by Richard Day Gore
Published by LaChance Publishing LLC
MSAA Book # 33

This is a collection of inspiring personal stories told by individuals with MS. The stories talk about the initial diagnosis of MS, what happens after diagnosis, living with MS, the MS family, and the gift of MS. Introductory sections include an overview of MS by Dr. John Richert, MD, and a written contribution from actress Teri Garr.

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